Alendronate and Estrogen–Progestin in the Long-Term Prevention of Bone Loss: Four-Year Results from the Early Postmenopausal Intervention Cohort Study

A Randomized, Controlled Trial

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Background: Up to 3 years of treatment with alendronate, 5 mg/d, prevents postmenopausal bone loss.

Objective: To determine whether the effect of alendronate is sustained at 4 years of treatment and persists after treatment is discontinued.

Design: Randomized, controlled trial.

Setting: United States and Europe.

Participants: 1609 postmenopausal women 45 to 59 years of age.

Intervention: Participants were randomly assigned to receive oral alendronate, 5 mg/d or 2.5 mg/d; placebo; or open-label estrogen–progestin. Women in the alendronate groups received alendronate for the first 2 years of the study. Treatment was then continued without change or replaced with placebo for the last 2 years of the study.

Measurements: Annual measurement of bone mineral density.

Results: By year 4, the bone mineral density of participants in the placebo group had decreased by 1% to 6% ($P < 0.001$). Four years of treatment with 5 mg of alendronate per day increased bone mineral density at the spine (mean change [±SE], 3.8% ± 0.3%), hip (mean, 2.9% ± 0.2%), and total body (mean, 0.9% ± 0.2%) ($P < 0.001$ overall). By year 4, bone mineral density at most skeletal sites was greater in participants who switched from alendronate to placebo than in those who continuously received placebo. In years 3 and 4, bone loss in participants who switched from alendronate to placebo was similar to that seen during years 1 and 2 in those who continuously received placebo. Compared with 5 mg of alendronate per day, estrogen–medroxyprogesterone acetate produced similar increases in bone mineral density and estradiol–norethisterone acetate produced increases that were substantially greater.

Conclusions: Four years of treatment with alendronate or estrogen–progestin prevented postmenopausal bone loss. A residual effect was seen 2 years after alendronate therapy was stopped; however, continuous alendronate treatment was more effective in preventing postmenopausal bone loss than 2 years of alendronate followed by 2 years of placebo.

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Osteoporosis is a serious disease that develops slowly over many years and results in fractures and associated health care costs (1–3). Available treatments increase bone mineral density and reduce the risk for fractures but do not fully restore bone mass or microarchitecture (4). Alendronate, a bisphosphonate that inhibits bone resorption but not bone mineralization (5), prevents bone loss, increases bone mineral density (6–10), and reduces the incidence of fractures at the spine and hip by 30% to 50% in postmenopausal women with osteoporosis (7, 11, 12). Because alendronate prevents bone loss, it can be used as an alternative to estrogen–progestin in the prevention of postmenopausal osteoporosis (13, 14). The optimal length and regimen of alendronate treatment, however, have not yet been determined. Long-term treatment is probably needed to substantially affect bone mass and achieve lasting prevention of bone loss. However, clinical trials must be done to address the continuing efficacy and safety of agents used for prevention of osteoporosis, including alendronate.

We compared the effects of 4 years of alendronate treatment or placebo on bone mass and bone turnover. We also evaluated the residual effects of alendronate after treatment was discontinued. A small comparison group of participants who received estrogen–progestin was included. Results of the first 2 years of the study were published elsewhere (13).

Methods

The Early Postmenopausal Intervention Cohort Study is a clinical trial of oral alendronate in 1609 postmenopausal women who were randomly assigned in a double-blind manner to receive alendronate, placebo, or open-label estrogen–progestin (13). Four study centers (two in the United States [Portland, Oregon, and Honolulu, Hawaii] and two in Europe [Nottingham, England, United Kingdom, and Copenhagen, Denmark]) are involved in this trial. Women in the alendronate groups received alendronate during the first 2 years of the study. Treatment

Table 1. Demographic Characteristics of the Study Sample at Year 2 and Distribution of Study Groups at Different Time Points

Characteristic	Placebo Group	Alendronate Group		Alendronate and Placebo Group		Estrogen–Progestin Group
		5 mg/d	2.5 mg/d	5 mg/d	2.5 mg/d	
Mean age ± SD, *y*	55 ± 4	55 ± 4	55 ± 4	56 ± 4	56 ± 4	55 ± 3
Mean time since menopause ± SD, *y*	8 ± 5	9 ± 6	8 ± 6	8 ± 5	8 ± 6	5 ± 3
Mean body mass index ± SD, kg/m^2	25 ± 4	26 ± 4	26 ± 4	27 ± 4	26 ± 4	25 ± 4
Mean bone mineral density at the lumbar spine ± SD, g/cm^2	0.92 ± 0.12	0.99 ± 0.13	0.96 ± 0.12	1.00 ± 0.14	0.95 ± 0.13	0.98 ± 0.12
Patients at baseline, *n (%)*	502 (31)	333 (21)	330 (21)	165 (10)	169 (11)	110 (7)
Patients included in the intention-to-treat analysis of bone mineral density at the lumbar spine, *n (%)*	461 (33)	285 (20)	294 (21)	126 (9)	136 (10)	102 (7)
Patients who completed 4 years of treatment, *n (%)*	368 (31)	226 (19)	243 (21)	120 (10)	131 (11)	82 (7)

was then continued without change or was discontinued and replaced with placebo for the last 2 years of the study (**Table 1**). All women treated with estrogen–progestin followed the same regimen for 4 years. The randomization schedule for the duration of the study was predetermined at baseline. The study was approved by the local ethics committees and institutional review boards.

Participants

We selected healthy women 45 to 59 years of age who were at least 6 months past menopause at study entry. Bone mineral density at the spine at baseline was 0.8 g/cm^2 or greater in approximately 90% of participants (13).

Treatment

Treatment was distributed across two strata. In stratum 1, women were assigned to receive 5 mg of oral alendronate per day, 2.5 mg of oral alendronate per day, placebo (Merck Research Laboratories, Rahway, New Jersey), or open-label estrogen–progestin. Dosages of alendronate were selected on the basis of results from previous dose-finding studies (10, 14). Prevention of bone loss or a slight increase in bone mineral density was the desired outcome. Participants in whom estrogen–progestin was contraindicated or unacceptable were enrolled in stratum 2, which did not include an estrogen–progestin group. In the United States, estrogen–progestin was given in a continuous combined regimen of conjugated equine estrogens, 0.625 mg/d (Premarin, Wyeth-Ayerst, Philadelphia, Pennsylvania), plus medroxyprogesterone acetate, 5 mg/d (Provera, Upjohn, Kalamazoo, Michigan). In Europe, estrogen–progestin was given in a cyclic combined regimen of micronized 17β-estradiol, 2 mg/d, for 22 days; norethisterone acetate, 1 mg/d, on days 13 to 22; and estradiol, 1 mg/d, on days 23 to 28 (Trisequens, Novo Nordisk, Lyngby, Denmark). Dietary calcium intake was estimated at baseline and at annual visits (13). All women whose calcium intake was lower than that dictated by the local standard of care were advised to increase their intake by changing their diet or by taking supplements.

Measurements of Bone Mineral Density and Biochemical Markers of Bone Turnover

Bone mineral density was measured at baseline and annually thereafter (QDR-2000, Hologic, Waltham, Massachusetts) (13). Fasting blood and urine samples (second morning void) were collected every 6 months. Bone resorption and formation were estimated by using urine N-telopeptide cross-links of type I collagen (Osteomark, Ostex, Seattle, Washington) corrected for creatinine excretion and serum osteocalcin (Human Osteocalcin Kit, Nichols Institute, San Juan Capistrano, California), respectively. In addition, the serum level of bone-specific alkaline phosphatase (Ostase, Hybritech, San Diego, California) was measured at baseline and at months 12, 24, and 36 in a random sample of 550 women.

Assessment of Treatment Safety

Participants were clinically evaluated every 3 months (13). All unfavorable and unintended clinical events, including fractures and abnormal laboratory values, were considered to be adverse events and were evaluated for severity, duration, and probable causal relation to study drug and outcome.

Statistical Analysis

Bone mineral density was analyzed by using an intention-to-treat approach in the 1404 participants who received the same treatment for 4 years and had a baseline measurement and at least one follow-up measurement and in participants who switched from alendronate to placebo and had at least one measurement during years 3 and 4. No data from years 1 and 2 were included in later analyses of participants whose treatment did not remain constant during the study.

Treatment effects were evaluated by using analysis of variance that included treatment, study center, stratum, and treatment-by-center interaction terms as factors. Interaction terms that were nonsignificant ($P > 0.10$) or nonqualitative were removed from the model. Between-treatment comparisons of least-squares means (adjusted for stratum and study center) were performed by using analysis of variance. Within-group changes were evaluated by using the pairwise t-test to examine whether the mean percentage changes differed significantly from 0. In the groups that received alendronate for 4 years, the progressiveness of the response with an increasing dose of alendronate was assessed by using the stepwise Tukey trend test, adjusted for multiplicity. In addition, subgroup analyses were performed according to years since menopause (<3 years, 3 to 9 years, and ≥10 years) and baseline bone mineral density at the spine (in all women and in women with osteopenia). All statistical tests were two-sided.

All between-group comparisons of placebo or alendronate and estrogen–progestin were performed within stratum 1. Estrogen–progestin regimens differed in U.S. and European centers; therefore, estrogen–progestin and alendronate were compared separately in each group by location of study center (United States or Europe). For graphical presentation, data from the groups receiving 4 years of alendronate or 2 years of alendronate followed by 2 years of placebo were pooled by dose during the first 2 years of the study because they were similar with respect to effect of treatment on bone mineral density and biochemical markers until that time. In the groups that received alendronate followed by placebo, a stepwise multiple regression analysis was used to compare cumulative bone loss in years 3 and 4 (after withdrawal of alendronate) with bone loss in years 1 and 2 in the group that continuously received placebo. Treatment, study center, stratum, bone mineral density at year 2, age, years since menopause, and body mass index were covariates of interest, and the least significant difference interval method was used to compare rates of cumulative bone loss.

Role of the Funding Source

Employees of Merck & Co., Inc., participated in the study as co-investigators. After designing the study with the input of the other study investigators, these employees implemented the protocol and coordinated data collection and statistical analyses. They also contributed to the writing of this paper, but data interpretation and decisions about the content of the paper and submission for publication resided with the entire group of investigators.

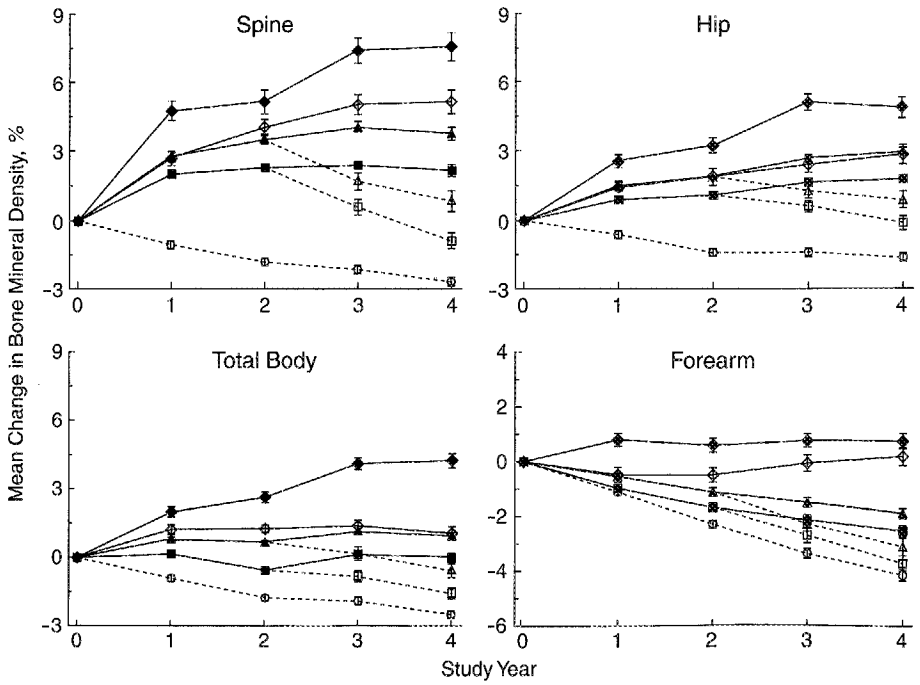

Figure 1. Mean percentage change (±SE) from baseline in bone mineral density at the lumbar spine, total hip, total body, and one-third distal forearm. Black triangles represent women who received 4 years of alendronate, 5 mg/d; black squares represent women who received 4 years of alendronate, 2.5 mg/d; white circles and dashes represent women who received 4 years of placebo; white diamonds represent women who received 4 years of estrogen–medroxyprogesterone acetate; black diamonds represent women who received 4 years of estradiol–norethisterone acetate; white triangles and dashes represent women who received 2 years of alendronate, 5 mg/d, followed by 2 years of placebo; and white squares and dashes represent women who received 2 years of alendronate, 2.5 mg, followed by 2 years of placebo. For graphical presentation, results from groups that received the same dosage of alendronate during the first 2 years of the study were pooled during this period for the two strata combined.

Table 2. Mean Percentage Change in Bone Mineral Density at Subregions of the Hip*

Subregion	Placebo Group	Alendronate Group		Alendronate and Placebo Group		Estradiol–Norethisterone Acetate Group	Estrogen–Medroxyprogesterone Acetate Group
		5 mg	2.5 mg	5 mg	2.5 mg		
	←			%			→
Femoral neck							
0–4 y	−2.9 ± 0.2†	1.4 ± 0.2†	0.6 ± 0.2‡	−1.3 ± 0.4§	−1.6 ± 0.4†	3.7 ± 0.6§	1.8 ± 0.5†
2–4 y	−1.5 ± 0.2†	0.1 ± 0.2	−0.1 ± 0.2	−2.2 ± 0.3§	−2.5 ± 0.3†	1.5 ± 0.5§	0.4 ± 0.5§
Trochanter							
0–4 y	−1.3 ± 0.2†	4.3 ± 0.3†	2.8 ± 0.3†	1.7 ± 0.4†	0.3 ± 0.4	6.9 ± 0.6†	4.3 ± 0.6†
2–4 y	−0.5 ± 0.2§	1.6 ± 0.2†	1.1 ± 0.2†	−1.4 ± 0.3†	−1.5 ± 0.3†	2.4 ± 0.5†	1.4 ± 0.5§

* Data are presented as the mean ± SE.
† $P < 0.001$.
‡ $P < 0.05$.
§ $P < 0.01$.

Results

All study groups had similar demographic characteristics at baseline; however, women in the estrogen–progestin group had experienced menopause more recently (**Table 1**). By the end of year 4, the relative proportion across treatment groups of women who had continued to participate in the study was similar to that at baseline (**Table 1**). Eighty-five percent of participants were white, 10% were Oriental (persons of Chinese, Japanese, and Korean descent), 1.4% were Asian (persons of Indian and Philippine descent), and less than 1% were from other ethnic groups.

Bone Mineral Density

Groups That Received the Same Treatment for 4 Years

In the placebo group, bone mineral density decreased at all skeletal sites (**Figure 1**, **Table 2**). Bone loss usually decreased as years since menopause increased. In contrast, 4 years of treatment with 5 mg of alendronate per day increased bone mineral density at the spine, hip, and total body and attenuated bone loss at the forearm (**Figure 1**, **Table 2**). Five mg of alendronate per day had a more pronounced effect on bone mineral density than did 2.5 mg of alendronate per day ($P < 0.01$). In both alendronate groups, bone mineral density at the spine, hip, and total body increased or remained unchanged during years 3 and 4 compared with year 2.

Compared with 4 years of treatment with 5 mg of alendronate per day, treatment with estrogen–medroxyprogesterone acetate resulted in greater increases in bone mineral density at the spine ($P < 0.001$) and similar increases at the hip ($P > 0.2$) and total body ($P > 0.2$) and was more effective in maintaining bone mass at the forearm ($P < 0.001$) (**Figure 1**, **Table 2**). Treatment with estradiol–norethisterone acetate also resulted in greater increases in bone mineral density at the spine ($P < 0.05$) and total body ($P < 0.001$) and similar increases at the hip ($P > 0.2$) and was more effective in maintaining bone mass at the forearm ($P < 0.001$) than treatment with 5 mg of alendronate per day.

The response to alendronate treatment was similar in the subgroup of women with osteopenia and in the total group (data not shown). Among women who received alendronate, bone mineral density increased in all subgroups according to years since menopause (<3 years, 3 to 9 years, or ≥10 years). However, increases were greater in women for whom more time had passed since menopause (data not shown).

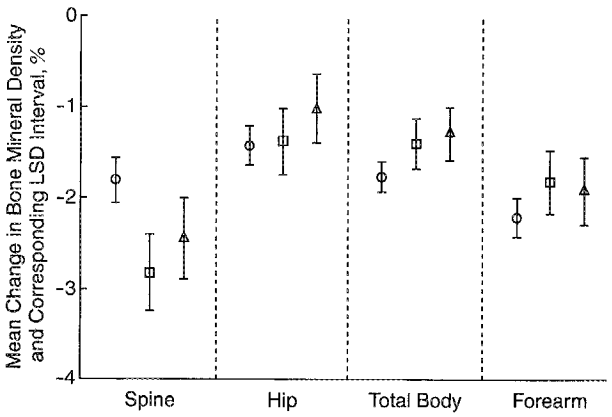

Figure 2. Cumulative percentage change and corresponding least significant difference (*LSD*) interval at the lumbar spine, total hip, total body, and one-third distal forearm. Changes from baseline to year 2 in the group that continuously received placebo are compared with changes in years 3 and 4 in the groups that did not continuously receive alendronate. Circles represent women who received 4 years of placebo; squares represent women who received 2 years of alendronate, 2.5 mg/d, followed by 2 years of placebo; and triangles represent women who received 2 years of alendronate, 5 mg/d, followed by 2 years of placebo. The LSD interval is approximately an 84% CI; overlapping LSD intervals imply that the *P* value exceeds 0.05 for between-group tests.

Groups That Received 2 Years of Alendronate Followed by 2 Years of Placebo

During years 3 and 4, bone mineral density decreased at all skeletal sites in participants who switched from alendronate to placebo ($P < 0.001$). The rate of bone loss in these participants during years 3 and 4 was similar to that observed during

years 1 and 2 in participants who continuously received placebo (**Figures 1** and **2**, **Table 2**).

By the end of year 4 of the study, 2 years of treatment with 5 mg or 2.5 mg of alendronate per day followed by 2 years of placebo had less of an effect on bone mineral density at all skeletal sites than 4 years of alendronate treatment but had a greater effect than 4 years of placebo (**Figure 1**, **Table 2**).

Biochemical Markers

Groups That Received the Same Treatment for 4 Years

In the placebo group, levels of *N*-telopeptide cross-links decreased slightly (**Figure 3**). In all other groups, levels of *N*-telopeptide cross-links decreased more than in the placebo group by month 6 and then decreased to within the normal premenopausal reference range (15, 16). Participants who received 5 mg of alendronate per day and those who received estrogen–progestin had similar dose-related decreases in levels of *N*-telopeptide cross-links, osteocalcin, and bone-specific alkaline phosphatase ($P < 0.001$).

Groups That Received 2 Years of Alendronate Followed by 2 Years of Placebo

During the placebo period, values for all biochemical markers increased toward baseline (**Figure 3**). By the end of year 4, levels of *N*-telopeptide cross-links were still significantly lower in the group that originally received 5 mg of alendronate per day than in the group that continuously received placebo ($P < 0.001$).

Adverse Events

In general, alendronate was well tolerated (**Table 3**). Only small differences in the number of clinical, drug-related, serious, or laboratory-related adverse events were observed between the groups that received alendronate and the group that received placebo. Furthermore, therapy was discontinued because of adverse events, as frequently in the alendronate groups as in the placebo group. The percentage of patients with upper gastrointestinal adverse events, including those that were considered to be related to the study drug, was also similar across all treatment groups.

One hundred thirty-one women had fractures during the study (153 nonvertebral fractures and 23 vertebral fractures), none of which were considered to be drug-related. No dose–response trend was seen in the number of fractures that occurred across treatment groups.

The safety and tolerability of both types of estrogen–progestin were different from those of alendronate and placebo. More than 88% of women receiving estrogen–progestin had at least one adverse event that was attributed to their therapy. The most

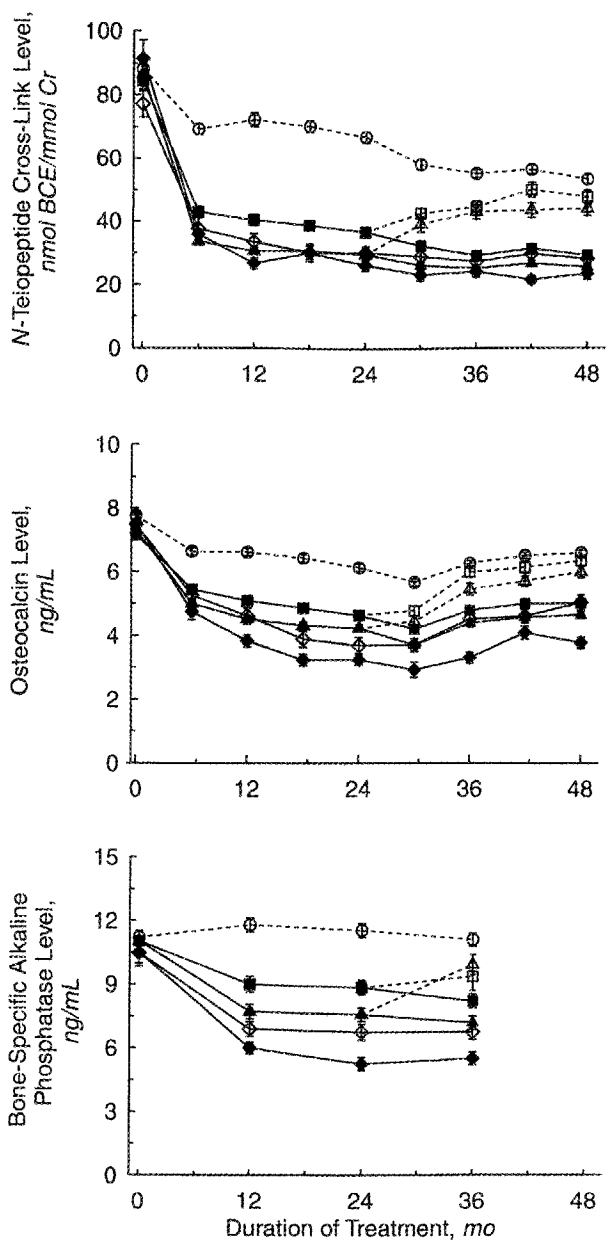

Figure 3. Mean observed change from baseline (±SE) in urine *N*-telopeptide cross-links of type I collagen, serum osteocalcin, and serum bone-specific alkaline phosphatase levels. Black triangles represent women who received 4 years of alendronate, 5 mg/d; black squares represent women who received 4 years of alendronate, 2.5 mg/d; white circles and dashes represent women who received 4 years of placebo; white diamonds represent women who received estrogen–medroxyprogesterone acetate; black diamonds represent women who received estradiol–norethisterone acetate; white triangles and dashes represent women who received 2 years of alendronate, 5 mg/d, followed by 2 years of placebo; and white squares and dashes represent women who received 2 years of alendronate, 2.5 mg/d, followed by 2 years of placebo. For graphical presentation, results from groups that received the same dosage of alendronate during the first 2 years of the study were pooled during this period for both strata combined. The mean premenopausal reference ranges (± SD) were 22.5 ± 9.4 nmol bone collagen equivalents (*BCE*)/mmol Cr for urine levels of *N*-telopeptide cross-links of type I collagen (15) and 8.8 ± 2.7 ng/mL for serum levels of bone-specific alkaline phosphatase (16). No premenopausal reference range was available for serum osteocalcin. To convert ng/mL to μg/L, multiply by 1.0.

Table 3. Adverse Events between Baseline and Year 4

Adverse Event*	Placebo Group (n = 502)	Alendronate Group		Alendronate and Placebo Group		Estrogen–Progestin Group (n = 110)
		5 mg (n = 333)	2.5 mg (n = 330)	5 mg (n = 165)	2.5 mg (n = 169)	
	n (%)					
Any	473 (94)	320 (96)	315 (96)	160 (97)	165 (98)	109 (99)
Drug-related event	63 (13)	36 (11)	50 (15)	26 (16)	15 (9)	97 (88)
Serious event†	62 (12)	45 (14)	48 (15)	24 (15)	22 (13)	13 (12)
System affected						
Cardiovascular	88 (18)	59 (18)	64 (19)	32 (19)	24 (14)	24 (22)
Musculoskeletal	369 (74)	238 (72)	245 (74)	128 (78)	129 (76)	71 (65)
Skin	239 (48)	153 (46)	156 (47)	71 (43)	76 (45)	51 (46)
Urogenital	222 (44)	139 (42)	162 (49)	76 (46)	67 (40)	104 (95)
Fracture	39 (8)	26 (8)	29 (9)	15 (9)	17 (10)	5 (5)
Upper gastrointestinal symptoms						
Any	197 (39)	131 (39)	144 (44)	76 (46)	63 (37)	41 (37)
Serious	3 (1)	3 (1)	2 (1)	3 (2)	0 (0)	1 (1)
Drug-related	38 (8)	24 (7)	33 (10)	15 (9)	8 (5)	12 (11)
Abdominal pain	82 (16)	48 (14)	45 (14)	23 (14)	29 (17)	16 (15)
Acid regurgitation	29 (6)	17 (5)	26 (8)	15 (9)	8 (5)	0 (0)
Dyspepsia	70 (14)	44 (13)	45 (14)	22 (13)	23 (14)	11 (10)
Nausea	54 (11)	32 (10)	32 (10)	22 (13)	15 (9)	11 (10)

* Adverse events could be classified in more than 1 category.
† Defined as death, permanent or substantial disability, cancer, life-threatening event, or an event requiring hospitalization.

commonly reported adverse events were withdrawal bleeding and breast tenderness.

Discussion

Four years of alendronate treatment prevented postmenopausal bone loss at the spine, hip, and total body and was more effective than 2 years of alendronate treatment followed by 2 years of placebo. In addition, increased bone mineral density at the spine, hip, and total body was maintained in women who received alendronate for 4 years. This suggests that a positive bone balance was attained (17, 18) and that bone loss did not resume during treatment with alendronate. Response to treatment with alendronate was similar in the subgroup of women with osteopenia and in the overall group. However, response to alendronate treatment was greater in women for whom more time had passed since menopause.

Treatment with estrogen–progestin produced changes in bone mineral density that were similar to those seen in previous studies (19–21). Treatment with estrogen–medroxyprogesterone acetate had a greater effect on bone mineral density at the spine and a similar effect at the hip and total body compared with 4 years of treatment with 5 mg of alendronate per day. Treatment with estradiol–norethisterone acetate resulted in greater increases in bone mineral density at all skeletal sites than did 4 years of treatment with 5 mg of alendronate per day. The superior effect of estradiol–norethisterone acetate was probably caused by the androgenic effects of the progestin in this formulation; norethisterone acetate alone is known to increase bone mass (22, 23). However, we did not formally compare the two estrogen–progestin regimens because of genetic differences in the drugs and environmental differences in the U.S. and European centers. In contrast to alendronate treatment, both regimens of estrogen–progestin fully maintained bone mass at the forearm.

In women who switched from alendronate to placebo at the end of year 2, the rate of bone loss at all skeletal sites during years 3 and 4 was similar to that observed in the placebo group during years 1 and 2. This comparison was considered to be the most appropriate, given that administration of placebo began at baseline in the placebo group and at year 3 in the groups that switched from alendronate to placebo. This approach has been used in studies of discontinuation of hormone replacement therapy (19). Because the 2-year time difference may have biased our results in favor of a slower rate of bone loss in groups that discontinued alendronate treatment, we included age and years since menopause as covariates of interest in the regression analysis of bone loss rates.

By the end of year 4, bone mineral density at the spine and hip remained above baseline in the group that received 5 mg of alendronate per day during years 1 and 2. This suggests a residual effect of previous treatment with alendronate, which may be caused in part by alendronate that is retained in the skeleton. Our results are consistent with recent reports of a modest residual effect observed up to 3 years after withdrawal of therapy with various doses of alendronate (8, 14, 24, 25). The therapeutic goal in postmenopausal women with normal bone mass

is to prevent bone loss and to maintain rather than increase bone mass. Two years of alendronate treatment followed by 2 years of placebo clearly fulfilled this goal, although treatment with alendronate for 4 years had a more pronounced effect.

After treatment with alendronate or estrogen–progestin, levels of biochemical markers of bone resorption and formation decreased into the premenopausal reference range. This indicates that alendronate and estrogen–progestin did not excessively suppress bone turnover (15, 16). Furthermore, the decrease in levels of biochemical markers seen during alendronate treatment was dose-related and was usually reflected in bone mineral density. When the groups that had been treated with alendronate were switched to placebo, the biochemical markers approached the levels seen in the placebo group. However, by the end of year 4, levels of *N*-telopeptide cross-links in the group that initially received 5 mg of alendronate per day before switching to placebo were significantly lower than those in the group that continuously received placebo. This is consistent with the minor residual effect in bone mineral density at the spine and hip that was observed in the group that received 5 mg of alendronate per day during the first 2 years.

During 4 years of treatment, alendronate (2.5 mg/d or 5 mg/d) was as safe and tolerable as placebo. We focused on the incidence of upper gastrointestinal adverse events because bisphosphonates can irritate the upper gastrointestinal mucosa when they are administered improperly or are given in higher doses (26). The number of upper gastrointestinal adverse events was similar in the alendronate and placebo groups, which indicates that gastrointestinal risk apparently did not increase during alendronate treatment.

Estrogen–progestin had a different safety profile than alendronate or placebo. However, safety data for nonblinded treatment groups should be interpreted cautiously because of the potential for reporting bias. The most frequently reported adverse events in the estrogen–progestin group were withdrawal bleeding and breast tenderness, which are common side effects of such treatment. It is important to note that, in contrast to previously reported results (27), these adverse events did not result in a higher rate of discontinuation of study participation in the estrogen–progestin group. This finding may reflect the possibility that for women in this group, who were closer to menopause, relief of postmenopausal symptoms outweighed the side effects of treatment.

Because the prevalence of osteoporotic fractures in a sample of healthy, recently postmenopausal women is low, reduction of risk for fractures was not a feasible end point in our study. In addition, 90% of the women studied were not osteoporotic at baseline and no immediate reduction in fracture risk was expected. Alendronate, 10 mg/d, has been shown to reduce the incidence of vertebral and hip fractures by approximately 50% in women with osteoporosis (11, 12), and observational studies and a few short-term longitudinal studies reported that opposed and unopposed estrogen treatment produced similar results (28–30). Because of the association between bone mineral density and susceptibility to fractures (31, 32), treatments that effectively maintain bone mass probably also provide long-term protection against fractures.

In conclusion, 4 years of treatment with alendronate or estrogen–progestin was more effective in preserving bone mass at the spine, hip, and total body than 2 years of treatment with alendronate because bone loss resumed when active treatment was discontinued. However, 2 years of treatment with alendronate also had a greater effect than placebo at the end of the 4-year study. Alendronate was usually well tolerated and can be used as an alternative to estrogen–progestin for prevention of postmenopausal osteoporosis.

Appendix

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